REMARKS

Claims 1 and 6-12 are currently pending in the application. Claims 1 and 6-12 are in independent form.

Applicants wish to express their appreciation for the courtesies extended Applicants' representative, Amy E. Rinaldo, during a telephonic interview conducted November 11, 2005.

Claims 2-5 and 13 stand rejected under 35 U.S.C. § 102(b) as being anticipated by the Moskowitz patent. Claims 2-5 and 13 have been canceled without prejudice thereby rending the present rejection moot. Reconsideration of the rejection is respectfully requested.

Claims 2-4 and 13 stand rejected under 35 U.S.C. § 102(b) as being anticipated by the Paluha et al. reference. As claims 2-4 and 13 have been canceled without prejudice, this renders the present rejection moot and reconsideration of the rejection is respectfully requested.

Claims 1-13 stand provisionally rejected under the judicially created doctrine of double patenting over claims 1-8 of co-pending application number USSN 10/075,715. An appropriately executed terminal disclaimer is enclosed herewith for overcoming this rejection. Reconsideration of the rejection is respectfully requested.

Claims 1-13 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Cunningham et al in view of Moskowitz and the Paluha et al. reference. Reconsideration of the rejection under 35 U.S.C. §103(a), as being unpatentable over the Moskowitz patent, the Poluha, et al. reference, and the Adams, et al. patent is respectfully requested.

The Office Action states that the Moskowitz patent teaches a method of treating strokes and the resulting neurological damage by administering nitric oxide releasing compounds. The therapeutic target of the Moskowitz approach is the reduction of cerebral infarction (i.e. volume of dead brain tissue) after ischemic stroke that is stroke caused by a lack of blood flow to the brain. Moskowitz seeks to increase blood flow to the brain to limit volume of infarction. In other words, the patent discloses treating injured brain in an attempt to salvage brain tissue. The

treatment disclosed in the Moskowitz patent is limited to times early after onset of ischemic stroke when blood flow increase can reduce the volume of blood flowing to the damaged tissue. In the Moskowitz patent, there is disclosed that the reduction of the infarction is mediated by administration of a substrate for NO before or early (within the first 1-2 hours) after stroke. The substrate is given from 16 hours before stroke to 2 hours after stroke. This enhances blood flow to the brain and thereby counteracts some of the loss of blood flow initiated by the stroke. The Moskowitz patent states in column 1 line 31 that, "the nervous system lacks the ability to regenerate," in column 1 lines 40- 44, "the ultimate size of the infarct, which forms the basis of medical therapy is the extent of vascular support." Thus, according to the Moskowitz patent, the intervention must be designed to improve blood flow and thereby to reduce the ischemic lesion, because when the lesion is complete, the lesion cannot be reduced by treatment there is no benefit.

The Moskowitz patent also discloses that the brain cannot regenerate. The data presented in the Moskowitz patent only relate to treatment of a model of ischemic stroke with a substrate of NO. All data presented by Moskowitz show a reduction of volume of cerebral infarction, dilation of blood vessels, and, as noted in column 3 line 18, the approach of the Moskowitz patent is to "limit the extent of stroke-associated infarct." The patent discloses that treatment should preferably begin shortly after the initiation of stroke and preferably at any point in time prior to the completion of the infarction process. There is disclosed that "treatment may be initiated, however, at any point in time prior to the completion of the infarction process." The disclosure also provides that "in certain instances, the methods of the invention may be used to treat a patient after the completion of a stroke episode." There is no disclosure of what those "instances" are or how they relate to treatment and thus, the disclosure does not enable one of skill in the art to ascertain the possibility that any beneficial effects are afforded a patient who has the NO compound administered post-stroke. Further, there is no disclosure that treatment at any point subsequent to the completion of the stroke would function in the desired manner. It is commonly known to those of skill in the art that there is a distinct period of time in which the damage occurring from a stroke can be mediated. Subsequent

to this time period, it was believed that treatment was futile. Further, the Moskowitz patent and all other prior art disclosures disclose methods for limiting the infarction process or increasing the blood flow to the areas of the brain that were damaged by stroke. There is no disclosure for the regeneration of neurons as is disclosed in the presently pending independent claims. There is also no disclosure for the use of other compounds that are not NO donors and do not form the substrate for NO.

In contradistinction, the presently pending independent claims claim therapeutic compounds including PDE5 inhibitors and related compounds, for inducing brain remodeling and restoring neurological function, completely independent of the effect of NO donors on the volume of infarction. As disclosed throughout the currently pending patent application and specifically claimed, the functional benefit is derived from treatment under conditions in which the volume of brain damage is unaltered by the treatment. Further, the claimed methods are used to treat and remodel viable brain. The method activates endogenous restorative mechanisms within the non-injured tissue, so as to compensate for the damage, and thereby to enhance neurological function. The therapy is designed to be given days and weeks after the injury, and the neurogenesis is totally independent of any affect of treatment of the lesion. The claimed method is specifically delayed until the completion of infarction, and can even be administered 24 or more hours after stroke. The method and compound of the presently pending independent claims claim inducing brain remodeling an event that is independent of the reduction of the volume of cerebral infarction. There is no connection or association of reduction of volume of cerebral infarction and with the production of new brain cells. There is no requirement of the presence of a NO donor to induce brain remodeling and functional benefit.

The Office Action has maintained that Applicants' definition of promoting neurogenesis includes proliferation of parenchymal cells and as such, is much broader than originally suggested. However, when read more specifically, the definition of promoting neurogenesis is defined as "new neuronal growth or enhanced growth of existing neurons, as well as growth and proliferation of parenchymal cells and cells that promote tissue plasticity." The neurogenesis occurs

as stated on page 7, lines 5-15 due to increased levels of cGMP resulting from the administration of the NO donor. The increased amount of cGMP increases the number of progenitor cells and the number of Tuj1 immunoreactive cells in the ischemic brain, thus enhancing the functional recovery after stroke. The recovery includes the increase of parenchymal cells as a result of the proliferation of new neurons, therefore, the parachymal cells are increased as a result of the neurogenesis. cGMP functions to increase neurons. Additionally, the methodology disclosed in the Moskowitz patent does not initiate neurogenesis. In fact, the Moskowitz patent discloses that neurons cannot regenerate. It is actually contrary to the common knowledge of those in skill in the art to have administered any compounds after the completion of the stroke. Instead, it was believed by those of skill in the art that upon completion of the stroke, an individual was no longer able to be treated and must instead learn to survive with the results of the stroke. Since the Moskowitz patent does not disclose or suggest the method and compound of the presently pending independent claims, the claims are patentable over the Moskowitz patent, and reconsideration of the rejection is respectfully requested.

As stated above, L-arginine is a well known substrate for nitric oxide based on simple chemistry. However, in the Moskowitz patent, L-arginine is used to evoke the production of NO in order to increase cerebral blood flow and thereby reduce lesion size. There is no discussion or suggestion for the use of NO to induce neurogenesis or to improve neurological outcome. Additionally, the claim recites other compounds that are not NO donors. Therefore, there is no teaching or suggestion in the Moskowitz patent for the claimed invention.

The Poluha, et al. reference, according to the Office Action, teaches a nitric oxide donor as a nerve growth factor for increasing neuron growth. The Poluha, et al. reference also teaches increasing levels of cGMP using NGF. However, when read more specifically, the Poluha, et al. reference teaches that nerve growth factor (NGF) blocks cell proliferation via a signaling cascade that involves NO and other factors. This is in direct contradistinction with the presently claimed invention, wherein there is disclosed and claimed that NO increases cell proliferation and the production of new neurons. While it is well known that neurotrophins such as NGF

increase neurite expression cell systems, neurite extension is not neurogenesis. Instead, the Poluha, et al. reference focuses on the differentiation of cells, i.e., change in the phenotype and not the production of new cells, i.e., neurogenesis. The abstract of the Poluha, et al. reference specifically states that nerve growth factor leads to the induction of nitric oxide synthase. Nitric oxide is not NGF. All that is noted on page 24005 is that cGMP levels increase in PC12 cells treated with NGF. There is no means for extrapulating that an NO donor, which increases cGMP, promotes the production of new brain cells or impacts neurological disease is any way. Instead, the reference discloses a linear pathway by looking at how NGF affects neurite outgrowth via a cell signaling pathway. Therefore, the Poluha, et al. reference does not disclose the claimed invention and reconsideration of the rejection is respectfully requested.

The Office Action acknowledges the Cunningham, et al. reference discloses methods of promoting neurogenesis by administering a neurotrophic factor or nerve growth factor. There is no disclosure of the invention as recited in the presently pending independent claims. It is respectfully submitted that there is no mention at all in the Cunningham, et al. reference that levels of cGMP are altered. Further, with regard to neurogenesis, the only mention of neurogenesis occurs with regard to Example 3, which relates to the survival of damaged neurons, not the development of new neurons. The neurogenesis referred to is specifically cited with regard to a period of gestation in which neurons are growing in the rats on which the testing occurred. Neuron growth and neurogenesis are two drastically different things. Neuron growth merely relates to the outgrowth of neurites, which is drastically different than neurogenesis, which is the growth of new neurons. Since there is no specific teaching of neurogenesis, it is respectfully submitted that the Cunningham, et al. reference does not at all relate to the presently claimed invention, nor does it disclose or suggest the invention as recited in the presently pending independent claims. Further, as stated above, the Moskowitz patent and Poluha, et al. reference, neither alone, nor in combination, teach the claimed invention. Accordingly, reconsideration of the rejection is respectfully requested.

Claims 1-13 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the Moskowitz patent, the Poluha, et al. reference, the Adams, et al. patent, and the Van Wagenen, et al. reference. Reconsideration of the rejection under 35 U.S.C. §103(a), as being unpatentable over the Moskowitz patent, the Poluha, et al. reference, the Adams, et al. patent, and the Van Wagenen, et al. reference is respectfully requested.

Specifically, the Office Action holds that Van Wagenen, et al. teaches that growth cones serve sensory and motor functions and L-arginine is a sensitizing agent. Therefore, it would have been obvious to combine the Moskowitz, Poluha, et al. and Adams, et al. teachings that administering NO effects neural growth with those of Van Wagenen, et al. Van Wagenen, et al. teaches that NO donors caused an elongation of filopodia and reduction of number of filopodia on the growth cones of snail neurons. Filopodia extend from the leading edge of a growth cone, aiding in the growth cone's navigational abilities, therefore serving sensory and motor functions *for the growth cone*. The filopodia are not involved in the overall motor and sensory functions of the brain and body. Van Wagenen, et al. teaches that low concentrations of NO acts as a cue that increases a neuron's growth cone action radius by the elongation of filopodia. (p. 183) Thus, NO donors can affect the ability of a growth cone to move toward a particular synapse to make a neuronal connection. Van Wagenen, et al. does not teach anything about neurogenesis or the recovery of function in the brain after a stroke or neural injury. There is no evidence that the mobility of existing growth cones can increase brain functionality or cognitive ability after a stroke or neural injury.

The presently pending claims are directed to increasing neural/cognitive function from neurogenesis and new neural growth. As described above, neurogenesis and new neural growth is unrelated to neurite outgrowth, wherein already existing neural growth cones navigate to associate with a particular synapse. Applying the teachings of Van Wagenen, et al. to the combination of Moskowitz, Poluha, et al. and Adams, et al. as discussed above, would only suggest that NO donors can increase growth cone mobility in a stroke victim, not that new neurons can be formed or that function can be recovered in the brain after a stroke or neural

injury. Therefore, the combination of Moskowitz, Poluha, et al. and Adams, et al. in view of Van Wagenen, et al. does not suggest a method of increasing neural or cognitive function from new neural growth by the administration of NO donors.

Since neither the cited references alone or in combination with knowledge in the art suggest the currently claimed invention, it is consequently respectfully submitted that the claims are clearly patentable over the combination, even if the combination were to be applied in opposition to applicable law, and reconsideration of the rejection is respectfully requested.

During the telephonic interview with the Examiner all of the pending claims were discussed. The Examiner had requested that a mode of administration be specifically detailed in the claims. After further review of the specification as filed that it was determined that multiple modes of delivery have been disclosed in the specification including, but not limited to, intravascularly, intraperitoneally, and orally. In light of the vast differences in modes of administration, it is respectfully submitted that restriction to a single mode of administration is not required and reconsideration of the oral rejection is respectfully requested.

The remaining dependent claims not specifically discussed herein are ultimately dependent upon the independent claims. References as applied against these dependent claims do not make up for the deficiencies of those references as discussed above. The prior art references do not disclose the characterizing features of the independent claims discussed above. Hence, it is respectfully submitted that all of the pending claims are patentable over the prior art.

In view of the present amendment and foregoing remarks, reconsideration of the rejections and advancement of the case to issue are respectfully requested.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

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CERTIFICATE OF MAILING

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